

## The Synthesis of a New Type of Anthracene DNA Intercalator

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**Abstract:** A new type of DNA intercalator based on anthracene **3** was synthesized. Preliminary binding studies show high affinity of this probe to CT-DNA. Higher binding constant of this compound ( $4.0 \times 10^4 \text{ M}^{-1}$ ) as compared with that known for 9-aminomethylantracene, is caused presumably by enhanced electrostatic interaction. © 1998 Elsevier Science Ltd. All rights reserved.

During our studies towards synthesis of a new type of DNA intercalating agent we turned our attention on anthracene derivatives.<sup>1</sup> It has been pointed out that anthracene-shape compounds intercalate without supporting positive charges with  $\Delta G_1 = 26\text{--}27 \text{ kJ/mol}$ .<sup>2</sup> When supporting aminoalkyl substituents are present this intercalation is enhanced by 5 kJ increment for each ion pairing. Indeed, 9-aminomethylantracene (**1**) binds to natural and synthetic DNA with high affinity.<sup>3</sup> Increased electrostatic interaction due to four positive  $\text{N}^+$  groups present in compound **2** (prepared by Czarnik and Van Aman) enhanced its intercalation to DNA.<sup>4</sup>

Since we were interested in a simple model for DNA ligand interaction studies, we turned our attention to compound **1**, which was difficult to be synthesized using the known methods.<sup>3,5</sup>

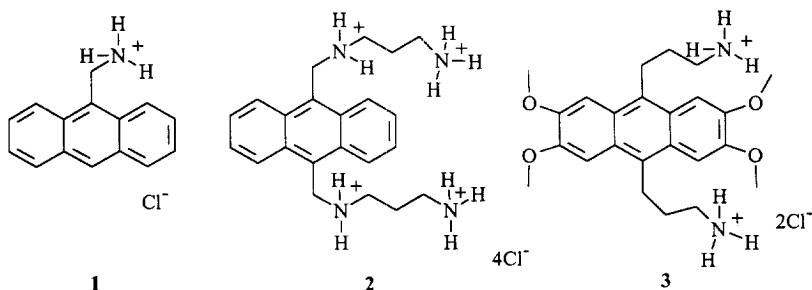


Chart 1

The synthesis of 9-aminomethylantracene (**1**) was performed using our own concept.<sup>6</sup> Unfortunately, compound **1** decomposes slowly in solution what reduces its potential application. Therefore we synthesised another type of compound of structure **3** possessing two amino groups and four methoxy groups. We turned our attention on reaction of aldehydes with veratrol catalyzed by sulfuric acid.<sup>7</sup> After many trials we found that direct acid promoted condensation of veratrol with 4-aminobutyraldehyd-diethyl acetal led to formation of aminoanthracene **3** in 55% yield.<sup>8</sup> For DNA binding studies hydrochloride of compound **3** was obtained.

Binding studies of **3** to DNA were performed using absorption and fluorescence spectroscopy. In the presence of increasing amount of CT DNA a strong decrease in the peak intensities (hypochromicity) was observed together with broadening and red shift in UV spectra.<sup>1</sup>

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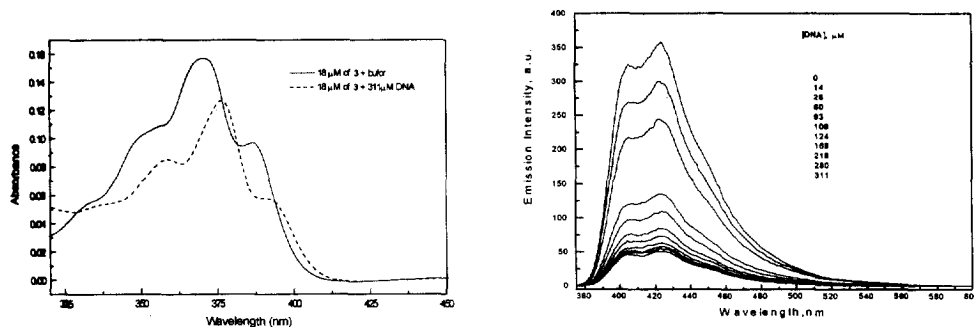


Figure 1. The changes in UV (left, dotted line) and fluorescence spectra of compound **3** ( $85 \text{ mmol dm}^{-3}$ ) upon addition of CT DNA (in  $50 \text{ mM NaCl}$  water solution, at  $\text{pH} = 7.0$ ).

Fluorescence studies proved that upon addition of CT DNA to the solution of **3** quenching of fluorescence by DNA bases was observed. Analysis of the fluorescence data according to Stern-Volmer equation<sup>3</sup> allowed us to calculate the binding constant of  $4.0 \times 10^4 \text{ M}^{-1}$ , which is higher than the value obtained for probe **1**<sup>3</sup> ( $1.0 \times 10^4 \text{ M}^{-1}$ ). Better binding of our probe to CT-DNA is probably enhanced by the electrostatic interactions due to the presence of the second amino group.<sup>2</sup> Functionalization of compound **3** and detailed studies of ligand-DNA interaction are in progress in our laboratories.

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- Commercially available 9-anthraldehyde was reduced by sodium borohydride to the corresponding alcohol in 88% yield. This compound reacted with  $\text{PBr}_3$  to afford 9-bromomethylantracene in 77% yield. Halogen substitution proceeds smoothly in DMSO containing  $\text{NaN}_3$ , at  $50^\circ\text{C}$  in 90% yield. Reduction was performed in THF solution at temperature below  $30^\circ\text{C}$  using  $\text{LiAlH}_4$ . Treatment of free amine in toluene with gaseous  $\text{HCl}$  precipitated pure hydrochloride **1**.
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- To the intensively stirred, cooled to  $5^\circ\text{C}$  solution of sulfuric acid (10 ml, 84%), a mixture of 4-aminobutyraldehyd-diethyl acetal (10 mmol) and veratrol (3 mmol) was added slowly, keeping temperature of the reaction mixture below  $10^\circ\text{C}$ . The reaction mixture was stirred at this temperature for 1 h. Then water (20 ml) was added followed by ammonium hydroxide to reach pH 11. Crude amine was extracted with chloroform, and purified by recrystallization from toluene. Hydrochloride **3** was precipitated from the chloroform solution after treatment of the amine with gaseous  $\text{HCl}$ . Overall yield 55%.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.99 (4H, br s,  $-\text{CH}_2\text{CH}_2\text{N}$ ), 3.10 (4H, t,  $J = 6.8 \text{ Hz}$ ,  $-\text{CH}_2\text{CH}_2\text{N}$ ), 3.46–3.58 (4H, m,  $\text{ArCH}_2-$ ), 4.02 (18H, br s,  $-\text{OCH}_3 + \text{NH}_3$ ), 7.41 (4H, s,  $\text{ArH}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.3, 28.2, 56.1, 96.0, 102.9, 125.5, 128.4, 149.6. Anal. Calcd. for  $\text{C}_{24}\text{H}_{34}\text{O}_4\text{Cl}_2 + \text{H}_2\text{O}$  57.26; H, 7.21; N, 5.56. Found: C, 57.02; H 7.50; N, 5.34.